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(74) Agents: BANNERMAN David, G. et al.; Withers & Rogers, Golding House, 2 Hays Lane, London, SE1 2HW (GB).

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(71) Applicant (*for all designated States except US*): KARO BIO AB. [SE/SE]; Novum, S-141 57 Huddinge (SE).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): MALM, Johan [SE/SE]; Bridgevagen 9B, S-142 66 Trangsund (SE). KOEHLER, Konrad [SE/SE]; Visatravagen 27, S-141 50 Huddinge (SE). GARCIA COLLARD, Ana Maria [SE/SE]; Moregatan 10, S-118 27 Stockholm (SE). GARG, Neeraj [SE/SE]; Barkvagen 15, S-145 52 Tumba (SE).

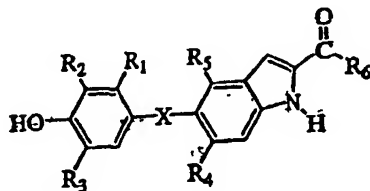
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(54) Title: IDOL DERIVATIVES AS NEW THYROID RECEPTOR AGONIST LIGANDS AND METHODS



(I)

(57) Abstract: This invention relates to novel compounds of the general formula (I), which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor Beta and to methods of preparing such compound. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T3 regulated gene, wherein a compound as described herein is administered in a therapeutically effective amount.

5

INDOL DERIVATIVES AS NEW THYROID RECEPTOR AGONIST LIGANDS AND METHODS

10

FIELD OF THE INVENTION

This invention relates to novel compounds that are thyroid receptor ligands and are preferably selective for the thyroid hormone receptor β . Further, the present invention
15 relates to methods for using such compounds and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

20 While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid hormone agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, obesity and cardiac
25 arrhythmias.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, the metabolic rate, body temperature, and mood, and influence serum low-density lipoprotein (LDL) levels.
30 Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In excess with hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

5 Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with L-thyroxine returns metabolic functions to normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T₄) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T₃). However, certain detrimental
10 effects from thyroid hormones may restrict replacement therapy, particularly in older individuals. In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially useful influences include weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to
15 utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular
20 and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid hormone receptor agonists that interact selectively with the β -form of the thyroid hormone receptor offer an especially attractive method for
25 avoiding cardio-toxicity.

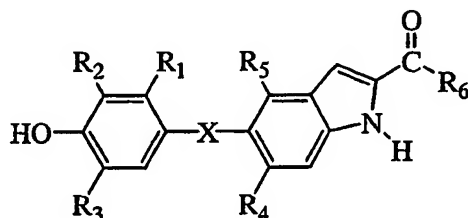
Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes, α and β . Further isoform differences are due to the fact that differential RNA
30 processing results in at least two isoforms from each gene. The TR α_1 , TR β_1 and TR β_2 isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the TR β_1 isoform is the most prevalent form in most tissues, especially in the liver and muscle. The TR α_2 isoform is prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as
35 a transcriptional repressor. The TR α_1 isoform is also widely distributed, although its

- 5 levels are generally lower than those of the TR β ₁ isoform. This isoform may be especially important for development. Whereas many mutations in the TR β gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TR α function have not been found.
- 10 A growing body of data suggests that many or most effects of thyroid hormones on the heart, and in particular, on the heart rate and rhythm, are mediated through the α -form of the TR α ₁ isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues, are mediated more through the β -forms of the receptor. Thus, a TR β -selective agonist might not elicit the cardiac rhythm and rate influences
- 15 of the hormones, but would elicit many other actions of the hormones. Applicants believe that the α -form of the receptor is primarily associated with heart rate function for the following reasons: (i) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TR β -forms, and high circulating levels of T₄ and T₃; (ii) there was a tachycardia in the only
- 20 described patient with a double deletion of the TR β gene (Takeda et al, *J. Clin. Endocrinol. & Metab.* 1992, 74, p49); (iii) a double knockout TR α gene (but not β -gene) in the mouse has a slower pulse than control mice (Forrest D and Vennstrom B, *Thyroid* 2000, 10(1), 41-52); (iv) western blot analysis of human myocardial TRs show presence of the TR α ₁, TR α ₂ and TR β ₂ proteins, but not TR β ₁. If these
- 25 indications are correct, then it may be possible that a TR β -selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (i) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (ii) replacement therapy in elderly subjects with subclinical hypothyroidism who are at
- 30 risk for cardiovascular complications; (iii) obesity; (iv) hypercholesterolemia due to elevations of plasma LDL levels; (v) depression; (vi) osteoporosis in combination with a bone resorption inhibitor.

5

SUMMARY OF THE INVENTION

In accordance with the illustrative embodiments and demonstrating features of the present invention, compounds are provided which are thyroid receptor ligands, and
 10 have the general formula I:



I

15 or a pharmaceutically acceptable salt thereof, wherein:

R₁ and R₂ is independently selected from: hydrogen; fluorine; chlorine; bromine; nitrile (-CN); C₁₋₂ alkyl, said alkyl substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different;

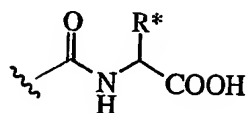
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R₃ is selected from the group: halogen; C₁₋₄ alkyl; C₃₋₄ cycloalkyl; C₂₋₄ alkenyl; C₂₋₄ alkynyl, said alkyl, cycloalkyl, alkenyl, alkynyl optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different;

25 R₄ and R₅ are the same or different and are independently selected from: hydrogen; chlorine; bromine; and C₁₋₄ alkyl;

R₆ is selected from: hydroxy (-OH); or an alpha amino acid linked to the carbonyl group (-CO-) via its nitrogen, thus forming an amide, the amine portion of the amide
 30 being derived from a natural (L) or unnatural (D) amino acid.

5 The amide mentioned above can be represented by:



10 and R* may be any of the side chains found in the naturally occurring alpha-amino acids;

R^a represents a member selected from: fluorine; chlorine; bromine;

15 X is selected from: -O-; -S-; -SO-; -SO₂-; -SO₂NH-; -SO₂O-;

The definition of formula I above includes all prodrug-esters, stereoisomers and pharmaceutically acceptable salts of formula I.

20 The compounds of formula I are thyroid hormone receptor ligands and include compounds which are, for example, selective agonists, partial agonists, antagonists or partial antagonists of the thyroid receptor. Preferably, the compounds of formula I possess activity as agonists of the thyroid receptor, preferably selective agonists of the thyroid receptor-beta, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, the compounds of formula I
25 may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T₃ regulated gene, such as obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, skin disorders or diseases and congestive heart failure.

30 The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. In particular, the present invention provides for a pharmaceutical composition

- 5 comprising a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

Further, in accordance with the present invention, a method is provided for preventing, inhibiting or treating the progression or onset of diseases or disorders
10 associated with the thyroid receptor, particularly, the thyroid receptor-beta, such as the diseases or disorders defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, i.e., human patient in need of treatment.

- 15 The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s) active in the therapeutic areas described herein.

In addition, a method is provided for preventing, inhibiting or treating the diseases as
20 defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of the invention and/or another type of therapeutic agent, is administered to a mammalian patient in need of treatment.

- 25 Compounds of the invention include, but are not limited to, the following:
4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E1);
4,6-Dibromo-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E2);
5-(4-Hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E3);
({1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl}-
30 amino)acetic acid (E4);
2-({1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl}-
amino)-3-methylbutyric acid (E5)

5 DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

10 The term "thyroid receptor ligand" as used herein is intended to cover any moiety, which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist. Another term for "thyroid receptor ligand" is "thyromimetic".

15 The term "alkyl" as employed herein alone or as part of another group refers to acyclic straight or branched chain radical, containing 1, 2, 3 or 4 carbons, preferable 1, 2 or 3 carbons in the normal chain, i.e. methyl, ethyl, propyl. When substituted alkyl is present, this refers to a straight or branched alkyl group substituted with 1, 2 or 3 groups of R^a, which groups may be the same or different at any available point, as defined with respect to each variable.

20 The term "substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which are commonly attached to such chains, such as, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino, halo, carboxyl or alkyl ester thereof and/or carboxamide, substituted or unsubstituted.

25 The term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2, 3 or 4 carbons and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present. Preferably 2 or 3 carbons are present in the normal chain radical, such as ethenyl and propenyl. As described above with respect to the "alkyl", the straight or branched portion of the alkenyl group may be optionally substituted by 1, 2 or 3 R^a which groups may be the same or different when a substituted alkenyl group is provided.

35 The term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 4 carbons and at least one carbon to carbon triple bond. Preferably one carbon to carbon triple bond is present. Preferably 2 to 3

- 5 carbons are present in the normal chain, such as ethynyl and propynyl. As described above with respect to "alkyl", the straight portion of the alkynyl group may be optionally substituted by 1, 2 or 3 groups of R^a which groups may be the same or different when a substituted alkynyl group is provided.
- 10 The term "cycloalkyl" as employed herein alone or as part of another group refers to saturated cyclic hydrocarbon groups or partially unsaturated cyclic hydrocarbon groups, independently containing one carbon-to-carbon double bond. The cyclic hydrocarbon contains 3 to 4 carbons. It should also be understood that the present invention also involve cycloalkyl rings where 1 to 2 carbons in the ring are replaced
- 15 by either -O-, -S- or -N-, thus forming a saturated or partially saturated heterocycle. Examples of such rings are aziridine, thiiranes and the like. Preferred heterocyclic rings are 3-membered, which may be optionally substituted by 1, 2 or 3 groups of R^a which groups may be the same or different through available carbons as in the case of "alkyl". Preferred cycloalkyl groups include 3 carbons, such as cyclopropyl, which
- 20 may be optionally substituted by 1, 2 or 3 groups of R^a which groups may be the same or different through available carbons as in the case of "alkyl".

The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically

25 acceptable) salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted,

30 for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids,

35 such as (C_1 - C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding

5 acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as
10 morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts that are unsuitable for pharmaceutical uses but which can be employed,
15 for example, for the isolation or purification of free compounds of formula I or their pharmaceutically acceptable salts, are also included. Preferred salts of the compounds of formula I which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. Preferred salts of the compounds of formula I which contain an acid group include sodium, potassium and
20 magnesium salts and pharmaceutically acceptable organic amines.

The compounds of formula I may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention.

25 Various forms of prodrugs are well known in the art. A comprehensive description of prodrugs and prodrug derivatives may be found in: (i) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996); (ii) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and (iii) *A Textbook of Drug*
30 *Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 – 191 (Harwood Academic Publishers, 1991). Said references are incorporated herein by reference.

Embodiments of prodrugs suitable for use in the present invention include lower alkyl
35 esters, such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM).

5 An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term “therapeutically effective amount” as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic
10 or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject’s size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not
15 useful to specify an exact effective amount in advance.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one
20 of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods. For example, chromatographic or fractional crystallization.

25

UTILITIES & COMBINATIONS

UTILITIES: The compounds of the present invention are thyroid receptor ligands, and include compounds that are, for example, selective agonists, partial agonists,
30 antagonists or partial antagonists of the thyroid receptor. Preferably compounds of the present invention possess activity as agonists of the thyroid receptor, preferably selective agonists of the thyroid receptor-beta, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, compounds of the present invention may be used in the treatment of diseases or
35 disorders associated with metabolism dysfunction or which are dependent upon the expression of a T₃ regulated gene.

5

Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to hypothyroidism; subclinical hyperthyroidism; non-toxic goiter; atherosclerosis; thyroid hormone replacement therapy (e.g., in the elderly); malignant tumor cells containing the thyroid receptor; papillary or follicular cancer; maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; eating disorders (e.g., anorexia); treatment of obesity and growth retardation associated with obesity; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of hyperinsulinemia; stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; treatment of congestive heart failure; treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; skin disorders or diseases, such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, and the prevention of dermal atrophy induced by topical glucocorticoids (such as the simultaneous treatment with topical glucocorticoid or a pharmacological product including both glucocorticoid and a compound of the invention), the restoration/prevention of dermal atrophy induced by systemic treatment with glucocorticoids, restoration/prevention of atrophy in the

5 respiratory system induced by local treatment with glucocorticoids, UV-induced
dermal atrophy, dermal atrophy induced by aging (wrinkles, etc.), wound healing,
keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis,
acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and
skin scarring.

10

The term treatment is also intended to include prophylactic treatment. In addition, the
conditions, diseases, and maladies collectively referenced to as "Syndrome X" or
Metabolic Syndrome as detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-
34 (1997), may be treated employing the compounds of the invention.

15

COMBINATIONS: The present invention includes within its scope pharmaceutical
compositions comprising, as an active ingredient, a therapeutically effective amount
of at least one of the compounds of formula I, alone or in combination with a
pharmaceutical carrier or diluent. Optionally, compounds of the present invention can
20 be used alone, in combination with other compounds of the invention, or in
combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or
other pharmaceutically active material.

The compounds of the present invention may be employed in combination with other
25 modulators and/or ligands of the thyroid receptor or other suitable therapeutic agents
useful in the treatment of the aforementioned disorders including: anti-diabetic
agents; anti-osteoporosis agents; anti-obesity agents; growth promoting agents
(including growth hormone secretagogues); anti-inflammatory agents; anti-anxiety
agents; anti-depressants; anti-hypertensive agents; cardiac glycosides;
30 cholesterol/lipid lowering agents; appetite suppressants; bone resorption inhibitors;
thyroid mimetics (including other thyroid receptor agonists); anabolic agents; and
anti-tumor agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds
35 of the present invention include biguanides (e.g., metformin or phenformin),
glucosidase inhibitors (e.g., acarbose or miglitol), insulins (including insulin

- 5 secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, glipizide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen
10 phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

- Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH
15 fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

- Examples of suitable anti-obesity agents for use in combination with the compounds
20 of the present invention include aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine)
25 reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), other thyroid receptor beta drugs, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), CB-1 (cannabinoid receptor) antagonists (see G. Colombo et al, "Appetite Suppression and Weight Loss After the Cannabinoid Antagonist SR 141716", Life
30 Sciences, Vol 63, PL 113-117 (1998)) and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

- The compounds of the present invention may be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins,
35 E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g.,

- 5 zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention may also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Patent No. 10 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HT_D 15 agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

- 20 A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999).

25 A further use of the compounds of this invention is in combination with steroidal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

- 30 Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as 35 mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists,

- 5 cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome
10 (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and
15 hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

20

For the treatment of skin disorders or diseases as described above, the compounds of the present invention may be used alone or optionally in combination with a retinoid, such as tretinoin, or a vitamin D analog.

- 25 Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide,
30 polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan
35 and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP)

- 5 inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

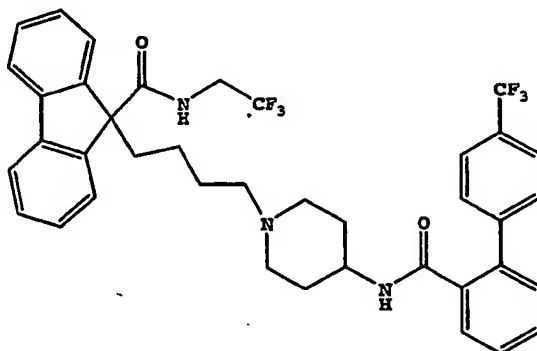
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- Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, an ileal Na⁺/bile acid cotransporter inhibitor, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

- MTP inhibitors which may be employed herein in combination with one or more compounds of formula I include MTP inhibitors as disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440 all incorporated herein by reference.

A preferred MTP inhibitor is

- 25 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide:



5 The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as
10 disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Further HMG CoA reductase inhibitors which may be employed herein include fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S.
15 Patent No. 4,613,610, indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-
20 hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin), as disclosed in
25 European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

The squalene synthetase inhibitors which may be used in combination with the compounds of the present invention include, but are not limited to, α -phosphono-
30 sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates, terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and
35 Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by

- 5 Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, as well as other squalene synthetase inhibitors as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

10

- Bile acid sequestrants which may be used in combination with the compounds of the present invention include cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL),
15 istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923,
20 quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

- ACAT inhibitors suitable for use in combination with compounds of the invention
25 include ACAT inhibitors as described in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, CI-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective
30 suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfanyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et
35 al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT

- 5 inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62.

Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those
15 disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

Examples of suitable ileal Na⁺/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

20

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens, β -agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostagladins, retinoic acid and compounds as disclosed in U.S. Pat. No. 3,239,345, e.g., Zeranol®; U.S. Patent No. 4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S. Pat. No. 4,411,890.

30

The aforementioned patents and patent applications are incorporated herein by reference.

The above other therapeutic agents, when employed in combination with the
35 compounds of the present invention, may be used, for example, in those amounts

- 5 indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Where the compounds of the invention are utilized in combination with one or more other therapeutic agent(s), either concurrently or sequentially, the following
10 combination ratios and dosage ranges are preferred:

When combined with a hypolipidemic agent, an antidepressant, a bone resorption inhibitor and/or an appetite suppressant, the compounds of formula I may be employed in a weight ratio to the additional agent within the range from about 500:1
15 to about 0.005:1, preferably from about 300:1 to about 0.01:1.

Where the antidiabetic agent is a biguanide, the compounds of formula I may be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 2:1.

20

The compounds of formula I may be employed in a weight ratio to a glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

- 25 The compounds of formula I may be employed in a weight ratio to a sulfonylurea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The compounds of formula I may be employed in a weight ratio to a thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about
30 0.5:1 to about 5:1. The thiazolidinedione may be employed in amounts within the range from about 0.01 to about 2000 mg/day, which may optionally be administered in single or divided doses of one to four times per day. Further, where the sulfonylurea and thiazolidinedione are to be administered orally in an amount of less than about 150 mg, these additional agents may be incorporated into a combined single tablet with a
35 therapeutically effective amount of the compounds of formula I.

- 5 Metformin, or salt thereof, may be employed with the compounds of formula I in amounts within the range from about 500 to about 2000 mg per day, which may be administered in single or divided doses one to four times daily.

- 10 The compounds of formula I may be employed in a weight ratio to a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-alpha/gamma dual agonist, an SGLT2 inhibitor and/or an aP2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1..

- 15 An MTP inhibitor may be administered orally with the compounds of formula I in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily. A preferred oral dosage form, such as tablets or capsules, may contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, administered on a regimen of one to four
20 times daily. For parenteral administration, the MTP inhibitor may be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, administered on a regimen of one to four times daily.

- 25 A HMG CoA reductase inhibitor may be administered orally with the compounds of formula I within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about
30 40 mg.

- A squalene synthetase inhibitor may be administered with the compounds of formula I within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will
35 contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

5

The compounds of formula I of the invention can be administered orally or parenterally, such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, in an effective amount within the dosage range of about 0.01 $\mu\text{g/kg}$ to about 1000 $\mu\text{g/kg}$, preferably about 0.1 $\mu\text{g/kg}$ to 100 $\mu\text{g/kg}$, more preferably about 0.2 $\mu\text{g/kg}$ to about 50 $\mu\text{g/kg}$ (or from about 0.5 to 2500 mg, preferably from about 1 to 2000 mg) in a regimen of single, two or four divided daily doses.

The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I can also be delivered through the oral cavity by sublingual

- 5 and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene
10 glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also
15 be added for ease of fabrication and use.

- Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other
20 solubilizing or dispersing agents such as those known in the art.

- Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's
25 solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

- Exemplary compositions for rectal administration include suppositories which can
30 contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

- Exemplary compositions for topical administration include a topical carrier such as
35 Plastibase (mineral oil gelled with polyethylene).

5 It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination,
10 and severity of the particular condition.

EXAMPLES

The following Examples represent preferred embodiments of the present invention.

15 However, they should not be construed as limiting the invention in any way. The ¹H NMR spectra were consistent with the assigned structures. Mass spectra were recorded on a Perkin-Elmer, API 150Ex spectrometer, with turbo "ion spray" on negative ion mode (ES-1) or positive (ES+1), using a Zorbax SB-C8 column (LC-MS).

20

4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E1)

(a) A suspension of dichloronitrophenol (1.8 g, 8.7 mmol) and triethylamine (1.33 mL; 9.56 mmol) in dichloromethane (60 mL) was added to a mixture of bis(3-
25 isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (6.7 g, 13 mmol) and Cu-bronze (1.1 g; 17.4 mmol) in dichloromethane (90 mL) at 0°C. The reaction mixture was stirred at room temperature under nitrogen gas for 3 days. The reaction mixture was filtered over celite and washed with dichloromethane. The resulted residue was purified by chromatography silica column (ethyl acetate/petroleum ether 1:9) to give
30 3.0 g (95%) of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)nitrophenyl.

(b) Stannous chloride dehydrate (9.9 g, 5.2 equiv.) was added to a solution of 3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)nitrophenyl (3 g, 8.45 mmol) in ethanol/ethyl acetate (200 mL, 1:1). The mixture was refluxed (80°C) overnight. After
35 30 minutes a yellow solid appeared. The reaction mixture was concentrated and ethyl acetate and water were added. The water phase was extracted with ethyl acetate (3

- 5 x50 mL) and the combined organic phases were dried with sodium sulfate. The resulted residue was purified by precipitation from a dichloromethane solution or by chromatography silica column (ethyl acetate/petroleum ether 1:5), to give 2.7 g (96 %) of 3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)phenylamine.
- 10 (c) A solution of 3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)phenylamine (934 mg, 2.9 mmol) in ethanol (2 mL) was added to hydrochloric acid (2.8 mL) cooled in an ice bath and the whole vigorously stirred. When the hydrochloride of the base separated as a thick solid, a solution of sodium nitrite (0.193 g of sodium nitrite in 0.84 mL of water) was added drop-wise, the stirring being continued and the reaction
- 15 mixture kept at 0°C. Everything turned red. A cooled solution of stannous chloride in hydrochloric acid (1.96g of stannous chloride in 1.68 mL of hydrochloric acid) was added slowly. After about 4 hours of stirring at 0°C a heavy, white precipitate was collected, well pressed and shaken with sodium hydroxide solution (2.5 mL of 25 %) and diethyl ether, and the ethereal layer separated. The aqueous solution was
- 20 extracted twice with ether, the combined ethereal extracts dried over potassium carbonate and the solvent was concentrated. The hydrazine formed in this way was dissolved in ethanol (22 mL) and acetic acid (9.35 mL), ethyl pyruvate (0.34 mL) and sulphuric acid (a couple of drops) were added. The mixture was heated at 80°C for 5 hours. Water was added, followed by extraction with ethyl acetate and the combined
- 25 organic extracts were dried with sodium sulfate and evaporation of the solvent. The resulting hydrazone was used in the next step without further purification. Polyphosphoric acid (3 mL) was added to the hydrazone and the mixture was heated at 120°C for 4 hours. Water was added and the mixture was taken to pH 7 by addition of sodium hydroxide (1 M). The water phase was extracted with ethyl acetate (3 x50
- 30 mL) and the combined organic phases were dried with sodium sulfate. The resulted residue was purified by chromatography silica column (ethyl acetate/heptane 1:5), to give 0.50 g (45 %) of 4,6-dichloro-5-(4-methoxy-3-isopropylphenoxy)-1H-indole-2-carboxylic ethyl ester. ¹H NMR (acetone-d₆, δ): 11.43 (s, 1H), 7.70 (s, 1H), 7.21 (s, 1H), 6.84 (d, J, 1H), 6.82 (d, J, 1H), 6.46 (dd, J, 1H), 4.39 (q, J, 2H), 3.77 (s, 3H),
- 35 3.34-33.21 (m, 1H), 1.37 (t, J, 2H), 1.14 (d, J, 6H). ¹³C NMR (acetone-d₆) δ 160.6,

5 152.2, 151.7, 141.2, 138.1, 134.2, 130.2, 126.4, 126.1, 121.3, 113.3, 112.8, 111.52, 111.29, 105.9, 61.0, 55.3, 26.8, 22.0, 13.7. LC-MS (ES-1): m/z 422 (M).

(d) To a dichloromethane solution of 4,6-dichloro-5-(4-methoxy-3-isopropylphenoxy)-1H-indole-2-carboxylic ethyl ester (330 mg; 0.8 mmol) cooled at -78°C ,
10 was added a solution of boron tribromide in dichloromethane (1 N; 2.3 mL). The mixture was allowed to reach room temperature slowly and it was stirred for 16 hours under nitrogen. The reaction was quenched by addition of ice and extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were dried with sodium sulfate, filtered and the solvent evaporated. The evaporated crude mixture was purified by
15 semi-preparative HPLC (acid system), to give 250 mg (80% yield) of 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic ethyl ester.

(e) A tetrahydrofuran solution of 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic ethyl ester (330 mg; 0.8 mmol) was treated with sodium
20 hydroxide (1 N, 5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was acidified with hydrochloric acid (1 N) and extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were dried with sodium sulfate, filtered and concentrated. The residue was purified by semi-preparative HPLC (acid system) to give 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-
25 carboxylic acid. ^1H NMR (acetone- d_6 , δ): 11.42 (s, 1H), 7.67 (s, 1H), 7.18 (s, 1H), 6.75 (d, J , 1H), 6.73 (d, J , 1H), 6.34 (dd, J , 1H), 3.33-3.21 (m, 1H), 1.14 (d, J , 6H). ^{13}C NMR (acetone- d_6 , δ): 161.6, 151.2, 149.4, 141.2, 136.0, 134.2, 130.0, 126.4, 121.3, 115.3, 113.2, 112.8, 112.7, 111.8, 106.0, 27, 22.0. LC-MS (ES-1): m/z 380 (M).

30

4,6-Dibromo-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E2)

This compound was prepared analogously and with similar yields as E1. Spectral and analytical data for 4,6-dibromo-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-
35 carboxylic acid: ^1H NMR (acetone- d_6 , δ): 11.43 (s, 1H), 7.90 (s, 1H), 7.15 (s, 1H), 6.82 (d, J , 1H), 6.80 (d, J , 1H), 6.44 (dd, J , 1H), 4.40 (q, J , 2H), 3.78 (s, 3H), 3.32-

- 5 3.21 (m, 1H), 1.38 (t, *J*, 2H), 1.14 (d, *J*, 6H). ¹³C NMR (acetone-d₆, δ): 151.0, 149.2, 143.1, 135.9, 128.8, 116.5, 115.2, 114.8, 113.3, 111.9, 110.6, 107.7, 27, 22.0. LC-MS (ES-1) *m/z* 469 (M).

5-(4-Hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E3)

10

A suspension of 5-hydroxy-2-carboxyindol ethyl ester (103 mg; 0.50 mmol) and triethylamine (56 mg, 0.55 mmol) in dichloromethane (10 mL) was added to a mixture of bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (382 mg; 0.75 mmol) and Cu-bronze (64 mg; 1.0 mmol) in dichloromethane (10 mL) at 0°C.

- 15 The reaction mixture was stirred at room temperature under nitrogen gas for 2 days. The reaction mixture was filtered through celite and washed with dichloromethane and concentrated. The residue was purified on column (silica gel, ethyl acetate/petroleum ether 1:9) to give 76 mg (52 %) of 5-(3-isopropyl-4-methoxyphenoxy)-2-carboxyindol ethyl ester.

20

- (b) To 5-(4-methoxy-3-isopropylphenoxy)-2-carboxyindol ethyl ester (43.5 mg; 0.10 mmol) in dichloromethane (5 mL) was added boron trifluoride dimethyl sulfide. The reaction mixture was stirred at room temperature for 10 hours and then treated with water, extracted with ethyl acetate and concentrated. The residue was purified on
25 column (silica gel), to give 29 mg (87 %) of 5-(4-hydroxy-3-isopropylphenoxy)-2-carboxyindol ethyl ester.

- (c) A tetrahydrofuran solution of 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic ethyl ester (330 mg; 0.8 mmol) was treated with Sodium
30 hydroxide (1 N, 5 mL) was added to a solution of 5-(4-hydroxy-3-isopropylphenoxy)-2-carboxyindol ethyl ester in methanol (5 mL). The mixture was stirred at room temperature for 3 hours. The reaction mixture was neutralized with hydrochloric acid (1 N) and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried over magnesium sulphate, filtered and concentrated. The residue was
35 purified on column (silica gel, chloroform/methanol/acetic acid, gradient elution from

5 1/0/0 to 95/5/0.5) to give 9 mg (39 %) of 5-(4-Hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid: ¹H NMR (methanol-d₄) δ 7.38 (d, J= 8.9, 1H), 7.26 (d, J= 2.2, 1H), 7.02 (s, 1H), 6.96 (dd, J= 2.2, J= 8.9, 1H), 6.80 (d, J= 2.7, 1H), 6.60 (d, J= 8.7, 1H), 6.60 (dd, J= 2.7, J= 8.7, 1H), 3.30 (m, 1H), 1.60 (d, J= 6.9, 6H).

10

((1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl)-amino)acetic acid (E4)

A solution of 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (300 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) (2 eq), 1-hydroxybenzotriazole hydrate (HOBT) (2.5 eq), in dimethyl formamide (20 mL) was stirred at room temperature for 0.5 hours followed by addition of a solution of glycine methyl ester hydrochloride (3 eq) and triethylamine (4.7 eq) in dimethyl formamide (5.0 mL). After stirring for 3 day, the reaction mixture was concentrated in vacuo. The resulted crude mixture was used without further purification. The crude mixture was hydrolyzed by treatment with 2 M aqueous sodium hydroxide in a mixture of methanol and THF. The evaporated reaction mixture was purified by semi-preparative HPLC (acid system), to give 180 mg (51% for two steps) of ((1-[4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl)-amino)acetic acid .

25

2-((1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl)amino)-3-methylbutyric acid (E5)

30 This compound was prepared analogously as E4. This Example was prepared from 15 mg of 4,6-dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid to give 26 % yield for the two steps.

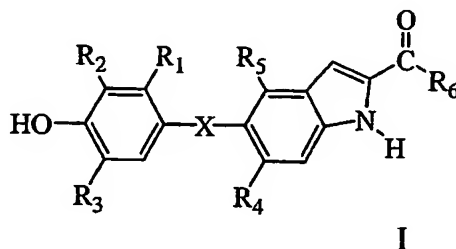
The compounds of Examples 1-5 exhibit binding affinities to the thyroid receptor beta in the range of IC₅₀ of 0.2 to 100 nM.

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CLAIMS

1. A compound of the general formula I:



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or a pharmaceutically acceptable salt thereof, wherein:

R_1 and R_2 is independently selected from: hydrogen; fluorine; chlorine; bromine; nitrile (-CN); C_{1-2} alkyl, said alkyl substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different;

15

R_3 is selected from the group: halogen; C_{1-4} alkyl; C_{3-4} cycloalkyl; C_{2-4} alkenyl; C_{2-4} alkynyl, said alkyl, cycloalkyl, alkenyl, alkynyl optionally substituted with 0, 1, 2 or 3 groups of R^a which groups may be the same or different;

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R_4 and R_5 are the same or different and are independently selected from: hydrogen; chlorine; bromine; and C_{1-4} alkyl;

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R_6 is selected from: hydroxy (-OH); or an alpha amino acid linked to the carbonyl group (-CO-) via its nitrogen, thus forming an amide, the amine portion of said amide being derived from a natural (L) or unnatural (D) amino acid.

30

R^a represents a member selected from: fluorine; chlorine; bromine;

- 5 X is selected from: -O-; -S-; -SO-; -SO₂-; -SO₂NH-; -SO₂O-;
- and pharmaceutically acceptable salts, prodrug ester forms and stereoisomers thereof.
- 10 2. A compound according to claim 1, which have one or more assymetric centers and can exist in the form of racemates, single and multiple enantiomers, as individual diastereomers, with all possible isomers, and mixtures thereof.
- 15 3. A compound according to claim 1 or 2 said compound being:
- 4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E1);
- 4,6-Dibromo-5-(4-hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E2);
- 20 5-(4-Hydroxy-3-isopropylphenoxy)-1H-indole-2-carboxylic acid (E3);
- ((1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl)- amino)acetic acid (E4);
- 25 2-((1-[4,6-Dichloro-5-(4-hydroxy-3-isopropylphenoxy)-1-H-indol-2-yl]methanoyl) amino)-3-methylbutyric acid (E5)
4. A compound according to any one of claims 1 to 3 for use in medical therapy.
- 30 5. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 to 3 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.
- 35 6. A process for making a pharmaceutical composition comprising combining a compound according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

- 5
7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 and at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite suppressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.
- 10
8. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a meglitinide, a sulfonylurea, a thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR alpha/gamma dual agonist, an SGLT2 inhibitor, a glycogen phosphorylase inhibitor, an aP2 inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor and insulin.
- 15
9. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride, glipryride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.
- 20
10. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an anti-obesity agent is selected from the group consisting of an aP2 inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor and an anorectic agent.
- 25
11. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is a hypolipidemic agent selected from the group consisting
- 30
- 35

- 5 of a thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal Na⁺/bile cotransporter inhibitor, a bile acid sequestrant and a nicotinic acid or a derivative thereof.
- 10 12. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T₃ regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claims 1 to 3.
- 15 13. The method according to claim 12, wherein the said disease is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.
- 20 14. The method according to claim 13, wherein the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
- 25 15. The use of a compound according to claims 1 to 3 in the preparation of a medicament for the treatment of a disease or disorder, which is dependent on the expression of a T₃ regulated gene.
- 30 16. The use according to claim 15 wherein said disease or disorder is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, and other endocrine disorders related to thyroid hormone.
- 35 17. The use according to claim 15 wherein said disease or disorder is a skin disorder, glaucoma, cardiovascular disease, or congestive heart failure.

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18. The use according to claim 17, wherein the skin disorder is dermal atrophy,
post surgical bruising caused by laser resurfacing, keloids, stria, cellulite,
roughened skin, actinic skin damage, lichen planus, ichthyosis, acne, psoriasis,
Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin
10 scarring.
19. A method to treat certain skin disorders or diseases by the use of a compound
of claims 1 to 3 in a combination with a retinoid or a Vitamin D analog.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08974

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/42 A61K31/404 A61P5/14 A61P9/06 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 297 833 A (PFIZER PROD INC) 2 April 2003 (2003-04-02) page 9, line 15 -page 10, line 12 page 29, line 13 -page 37, line 54 page 44, line 1 - line 6; claims; examples ---	1-19
X	WO 02 051805 A (FAESTE CHRISTIANE ;VOEHRINGER VERENA (DE); WOLTERING MICHAEL (DE);) 4 July 2002 (2002-07-04) page 42, line 1 - line 9; claims; examples ---	1-19
X	WO 01 70687 A (FAESTE CHRISTIANE ;PERNERSTORFER JOSEF (DE); VOEHRINGER VERENA (DE) 27 September 2001 (2001-09-27) claims page 45, line 24 -page 46, line 2; examples --- -/--	1-19

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 December 2003

Date of mailing of the international search report

12 12 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

GERD STRANDELL /EÖ

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08974

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WO 02 062780 A (GRIVAS SPIROS ;LI YI-LIN (SE); FLOEISTRUP ERIK (SE); KAROBIO AB (S) 15 August 2002 (2002-08-15) page 13, line 10 -page 15, line 26; claims; examples</p> <p>-----</p>	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08974

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-14 and 19
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 12, 15 all in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 12-14 and 19

Claims 12-14 and 19 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions. These alleged effects must be well defined diseases or conditions.

Continuation of Box I.2

Claims Nos.: 12, 15 all in part

The expressions "a disease which is dependent on the expression of a T 3 regulated gene or associated with metabolic dysfunction" and "a disease or disorder which is dependent on the expression of a T 3 regulated gene in claims 12 and 15 may relate to a number of different disorders and conditions, which can not be clearly defined by these expressions. Thus, the search has mainly been restricted to the diseases mentioned in claims 13-14 and 16-19, respectively.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08974

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1297833	A	02-04-2003	BR 0203877 A	16-09-2003
			CA 2404848 A1	26-03-2003
			EP 1297833 A1	02-04-2003
			JP 2003160559 A	03-06-2003
			US 2003078289 A1	24-04-2003

WO 02051805	A	04-07-2002	DE 10130830 A1	25-07-2002
			CA 2433100 A1	04-07-2002
			WO 02051805 A1	04-07-2002
			EP 1347959 A1	01-10-2003
			US 2003078288 A1	24-04-2003

WO 0170687	A	27-09-2001	DE 10065434 A1	14-03-2002
			AU 6211301 A	03-10-2001
			CA 2403806 A1	20-09-2002
			WO 0170687 A1	27-09-2001
			EP 1268422 A1	02-01-2003

WO 02062780	A	15-08-2002	CA 2435820 A1	15-08-2002
			WO 02062780 A2	15-08-2002
			EP 1358175 A2	05-11-2003
